REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not introduce any new claims; does not raise any new issue requiring further search and/or consideration, because the amendments amplify issues previously discussed throughout prosecution, and places the application in better form for an appeal should an appeal be necessary.

1. Summary

The Office Action Summary reflects that claims 1, 2, 6, 7, and 48-67 are pending and stand rejected. The Summary also indicated that the drawings are accepted.

Applicants have amended claims 6, 7, and 67. No prohibited new matter is believed to have been introduced by entry of the amendments, because the claims are supported at least by the claims as originally filed. Applicants reserve the right to file a continuation or divisional application on any subject matter cancelled by way of this amendment.

2. Status of Prior Rejections

The Office states on page 2, second paragraph, that any rejections not reiterated in this action are withdrawn. Therefore, the rejections under 35 U.S.C. § 112, second paragraph of claims 2, 52, 54-57, and 61 on pages 3-4 are withdrawn. Likewise, the rejections under 35 U.S.C. § 112, first paragraph of claims 1, 2, 6, 7, and 48-61 stand withdrawn.

3. Improper Final Rejection

To issue a final rejection under 37 C.F.R. § 1.113(b), it is required that "the examiner shall repeat or state all grounds of rejection then considered applicable to the claims in the applications, ***clearly stating*** the reasons in support thereof." (Emphasis added). Although the Office may refer to a complete statement of a ground of rejection made in a previous Office Action, the Office should also include a rebuttal of any arguments raised in applicant's reply and these arguments should clearly set forth the reason for rejection. *See* M.P.E.P. 706.07.

Applicants assert that the final rejection is improper because the presented arguments are incomplete in view of Applicants' amendments to the claims and introduction of new claims. On one hand, the Office states that the claims are rejected "for the reasons

of record as set forth in the Office Action mailed 2/24/05" for both the combined rejections under 35 U.S.C. §§ 101 and 112, first paragraph and the 35 U.S.C. § 112, first paragraph (enablement) rejection. *See* Office Action pages 3-4. No mention is made on these pages of the amendments to the claims, the new claims, or the Office's response to Applicants' arguments that is set forth on pages 4 to 13. Additionally, in the response to arguments for the enablement rejection, the Office states that part of the rejection of the claims has been overcome. *See* Office action, page 9. Thus, the rejection status of the claims is incomplete.

At no time does the Office specifically address why the new claims (*i.e.* claims 62-67), which were introduced by the August 23, 2005 response, were rejected. The new claims were apparently lumped in with the other claim rejections. The new claims did not exist at the time of the February 24, 2004, Office Action. M.P.E.P. § 706.07 sets forth that reference to a single prior Office Action in a future Office Action is permissible if it is a complete statement. However, in view of the new claims and claim amendments, it is unclear how the prior Office Action can serve as a ***complete*** statement. Additionally, Applicants direct the Office's attention to M.P.E.P. § 707.07 (d) which states that omnibus rejections of claims for the reasons of record should be avoided. Therefore, Applicants assert that 37 C.F.R. § 1.113(b) has not been met and the finality of the rejection is improper. Applicants respectfully request withdrawal of finality of the Action and in the event the rejection is maintained, that the Office provide detailed reasons explaining why the rejection stands in view of the claim amendments and new claims.

4. Information Disclosure Statements

Applicants note that they have not received an acknowledge PTO Form 1449 back for the Information Disclosure Statement submitted July 14, 2004 (4th Information Disclosure Statement). Applicants submit herewith a copy of the form for acknowledgement and return.

5. Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 6, 7, and 67 stand rejected as indefinite. Claims 6 and 7 stand rejected for the recitation of "the candidate molecule". Claim 67 depends from claim 6. Office Action, page 2.

Applicants have amended claims 6 and 7 to remove "the candidate molecule" and to refer, as appropriate, to "the reagent", as suggested by the Examiner. The amendments to claims 6 and 7 (and thereby to claim 67) obviate the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims 6, 7, and 67.

6. Rejection under 35 U.S.C. §§ 101 and 112, First Paragraph

6.1 Rejection under 35 U.S.C. § 101

Claims 1, 2, 6, 7, and 48-67 stand rejected under 35 U.S.C. § 101, because allegedly these claims are not supported by either a credible, substantial, and specific asserted utility or a well-established utility for the reasons of record as stated in the Office Action dated February 24, 2005. Office Action, page 3.

In the section entitled "Response to Arguments," on page 6-7 of the Office Action, the Office states:

> The instant claims are drawn to a method of identifying a reagent that "modulates a lipid." This is in contrast to the previous claims which were drawn to a method for identifying a molecule involved in lipid regulation. It was previously indicated that the term "involved" in the previous claims was vague and did not indicate how the molecule was involved in lipid regulation. In the instant case, although the term "involved" has been deleted from the claims, identifying a reagent that "modulates" a lipid still does not have a specific and substantial utility because further experimentation would be required. That is, completing the claimed method would result in the identification of a reagent that presumably "modulates" a lipid; however, without any indication what modulates encompasses (and without an indication of which lipid the reagent modulates), further experimentation would be required in order to determine a "real world" use for the identified reagent.
>
> Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context for use for the claimed method. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Therefore, the assertion that Zmax1 and HBM are members of the lipid receptor family of proteins, even in view of the cited art, does not establish a substantial or real world use for the claimed method because once the method is completed additional experimentation would be required. Thus, the present disclosure is only a starting point for further research and investigation into potential practical uses of the claimed polypeptides.

Another contention that the Office appears to assert surrounds the use of the word "modulates" in the amended claims. The Office argues that "modulating a lipid" is not a specific and substantial utility, and thus the claimed method cannot have a specific and substantial utility. *See*, Office Action page 8, first para. The Office also states that "[t]his is a the case with the instant method where the claims of identifying a reagent that modulates a

lipid, without any indication 'modulates' encompasses or even which lipids the reagent would 'modulate' do not fully disclose a 'real world' utility." Office Action, para. bridging pages 7-8.

A third argument is posited on page 8 of the Office Action, which states the following with regard to the HBM and Zmax1 proteins:

> It is acknowledged that the applicants have asserted that the HBM and Zmax1 proteins are members of the LDL receptor family of proteins. However, as previously indicated, simply because a protein may happen to be an LDL receptor is no indicative of any particular function for the protein (or any reagent that interacts with it), as the prior art recognizes that lipid receptors can have a plethora of different functions in a cell. However, the specification and the art of record do not indicate any particular function for the Zmax1 and HBM proteins. Therefore, at best, the specification has merely identified Zmax1 and HBM, in general, as being lipid receptors without identifying how they are involved in modulating lipids. Therefore, using Zmax1 and HBM in methods of identifying reagents that modulate a lipid are not specific because any member of the lipid receptor family could be used to identify a reagent that "modulates" a lipid.

6.2 Status of the Rejection

Applicants traverse the rejection. Respectfully, it is unclear how the utility requirement can be maintained for reasons of record, when Applicants amended the claims and added new claims. The reasons why the new claims are specifically rejected also is not addressed.

Applicants maintain that no *prima facie* case for lack of utility has been adduced, because (1) there is a function for Zmax1 and HBM as spelled out in the literature and specification; (2) modulation of a lipid in a screening assay has a specific and substantial utility; and (3) the term "modulation" is clear. Thus, Applicants maintain that a specific and substantial utility, if not a well-established utility, exists for the claimed methods.

6.2.1 There is an ascribed function for Zmax1 and HBM

As discussed fully above, the Office argues on page 8 that "[h]owever, the specification and the art of record do not indicate any particular function for the Zmax1 and HBM proteins." Applicants disagree.

The Office did not rebut that HBM is an allelic variant of Zmax1 (LRP5 is another name for the wild-type gene). Nor did the Office rebut Applicants' arguments on page 11 of the August 23, 2005 response, which stated that the nucleic acids encoding the HBM and Zmax1 polypeptides are not from separate genes involved in separate signaling cascades.

Thus, the Office appears to accept this assertion. In fact, the Office acknowledges that "HBM has been associated with lower triglycerides/VLDL levels and a better LDL:HDL ratio compared to controls." Office Action, page 11.

Applicants have asserted that the specification ascribes a function to Zmax1 and HBM. For example, Zmax1 and its polymorphic variant, HBM, are involved in bone modulation. Additionally, Applicants provide data "in Example 3 of the specification that demonstrates that the HBM variant when expressed in humans is correlated to an altered lipid profile. The tabulated data of Example 3 presents profiles for affected members having the HBM variant (marked 'A') and profiles of unaffected members having Zmax1, i.e. wt-LRP5 (marked "U")." August 23, 2005 Response by Applicants, page 11.

In addition to the assertion in the specification that Zmax1 and HBM are involved in lipid regulation, there is also substantial support in the literature. Thus, Applicants also disagree with the Office's conclusion that the art of record does not ascribe a function for the Zmax1 or HBM proteins.

6.2.1.1 Fujino et al.

T. Fujino et al., 2003 "Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion," *Proc. Nat'l Acad. Sci.* 100(1): 229-234 ("Fujino") clearly provides a function to LRP5. LRP5 and Zmax1 are synonyms. The title of the reference alone ascribes a function to LRP5: ***"Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion."*** This paper was submitted and accepted by the *Proceedings of the National Academy of Sciences*. The paper was edited and approved by Michael S. Brown. *See* Fujino et al., at 229. Michael S. Brown and Joseph L. Goldstein received the 1985 Nobel Prize in physiology or medicine for their discovery of the mechanism by which cholesterol accumulates in the bloodstream, leading to atherosclerosis. Additionally, both Drs. Brown and Goldstein provided comments during the review of the manuscript leading to the Fujino et al. paper. *Id.*, at 234, right column.

Fujino lays out that LRP5 can bind apolipoprotein E (apoE) and cite to Reference No. 18 (*i.e.*, D. Kim et al., 1998 *J. Biochem (Tokyo)* 124: 1072-76). Fujino, at 229, right column. The authors also state "LRP5 is a multifunctional receptor involved in multiple pathways, including bone development, cholesterol metabolism, and the modulation of glucose-induced insulin secretion." *Id.* The authors go on to state that "LRP5 is ***required*** for proper hepatic

clearance of chylomicron remnants and for glucose induced insulin secretion from the pancreatic islets, in addition to bone and eye development." *Fujino et al.,* at 233, right col. (Emphasis added).

Therefore, Fujino reference alone provides a role for LRP5 (Zmax1). Therefore, a particular function is ascribed to Zmax1, contrary to the Office's position.

6.2.1.2 Magoori

In K. Magoori et al., 2003 "Severe hypercholesterolemia, impaired fat tolerance and advanced atherosclerosis in mice lacking both LDL receptor-related protein 5 (LRP5) and Apolipoprotein E," *J. Biol. Chem.* 278(13): 11331-11336 ("Magoori"), the authors reiterated their findings as stated in Fujino et al. (2003). *See* Abstract and Discussion on 11331 and 11335, respectively. The authors concluded that the "data suggest that LRP5 mediates both apoE-dependent and apoE-independent catabolism of plasma lipoproteins." *See* Abstract, page 11331. The authors also stated that "LRP5 modulates the plasma clearance of diet-derived triglycerides in the absence of apoE by stimulating the hydrolysis of triglycerides." Magoori, at 11335, right col., first para.

Applicants further note that Magoori states that screening models and assays involving LRP5 are useful. For example, the authors state that the apoE/LRP5 double knockout mice manifesting the extreme hypercholesterolemia and advanced arthrosclerosis will provide a useful animal model for research and development of therapeutic agents against hypercholesterolemia and atherosclerosis. *See* Magoori at 11335. These authors support the contention that modulation of a lipid through the LRP5 mechanism and screening models therefore have a well-established utility. This is an aspect of the instant claims. Therefore, the claims have at least a specific and substantial utility, if not a well-established utility.

6.2.2 Modulation of a lipid in a screening assay has a specific and substantial utility

On page 6, the Office contends that all the pending claims lack utility, because identifying a reagent that "modulates" a lipid does not have a specific and substantial utility as further experimentation is allegedly necessary in order to determine a "real world" use for the identified reagent. Office Action, page 6, first full para. The Office goes on to say that "completing the claimed method would result in the identification of a reagent that presumably modulates a lipid; however, without any indication what modulates encompasses (and without an indication of which lipid the reagent modulates), further

experimentation would be required in order to determine a "real world" use for the identified reagent." *Id.*

Applicants traverse the rejection. Modulation of a lipid, such as HDL, VLDL, cholesterol, or apoE via Zmax1 or a Zmax1 variant (if not well-established) is a specific and substantial utility as discussed *supra*. An entire industry of lipid-regulating drugs has evolved (*e.g.*, statins such as Lipitor, Zocor, Baycol, and Pravachol; bile acid sequestrates such as Colestid and Questran; nicotinic acid; and fibric acids). Therefore, methods of screening new compounds and new classes of reagents to identify those with a lipid regulating activity has a specific and substantial, if not well-established, utility.

Addressing the rejection as to each of the claims, Applicants note that claim 1 is a method of identifying a reagent that modulates a lipid requiring (a) exposing said reagent to a Zmax1 or HBM, (b) determining binding of reagent to Zmax1/HBM; and (c) administering said reagent to an animal and determining whether a lipid is modulated. Claims 2 and 48-66 depend directly or indirectly from Claim 1. Thus, claims 1, 2, and 48-66 are directed to a method of determining whether a specific drug modulates a lipid in an animal. Regarding claim 6 (and dependent claims 7 and 67), the method for identifying a reagent modulating lipid is one that involves binding to a nucleic acid of Zmax1, measuring the binding, and measuring and comparing the binding of the reagent to various sequences, and administering it to a cell to determine modulation of a lipid in the cell (as amended). There is a real world use for screening reagents that modulate a lipid in an animal as indicated by Magoori. Whether further experimentation may or may not be required for the identified drug for purposes of obtaining FDA approval or characterization of the reagent is not pertinent to the issue of whether the claimed method of identifying reagents has a utility.

Regarding the Office's comment of "without an indication of which lipid the reagent modulates", Applicants point out that claims 66 and 67 both list a triglyceride or a VLDL, which are modulated. Applicants therefore submit that the Office improperly argues that all the claims are directed to any lipid. This argument should respectfully be withdrawn.

The Office asserts that the claims fall within the category of invention as set forth under M.P.E.P. § 2107.01(C). Applicants disagree. The method of screening steps provided identify a compound that would have a specific and substantial activity: a method of identifying reagents that modulate a lipid in an animal. This section of the M.P.E.P. goes on to say that "[m]any research tools such as...screening assays...***have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds).***" This is a

research tool for analyzing compounds that can bind to Zmax1 and/or HBM and also have lipid modulating activity. As such, the claims have utility.

6.2.3 The term "modulation" is clear

There is no outstanding rejection of the term "modulation" or "modulating" as indefinite or lacking written description. Additionally, the term is sufficiently described and would have been understood at the time the application was filed, as well as today as to its meaning. Accordingly, the Office's assertion on page 8 regarding what "modulates" encompasses is not pertinent to the 35 U.S.C. § 101 rejection.

6.3 Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 6, 7, and 48-67 also stand rejected under 35 U.S.C. § 112, first paragraph, because "the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons ***set forth above,*** one skilled in the art clearly would not know how to use the claimed invention, for the reasons of record as set forth in the Office Action mailed 2/24/05." *See* Office Action, page 3 (Emphasis added).

Applicants traverse the rejection. Respectfully, it is unclear how the combined 35 U.S.C. §§ 101 and 112, first paragraph enablement requirement can be maintained for reasons of record, when Applicants amended the claims and introduced new claims. Additionally, there is no portion of the "Response to Arguments" on pages 4 to 9 which are specifically directed to the § 112, first paragraph – enablement portion of the combined rejection. Applicants assert that a *prima facie* case of lack of enablement has not been adduced by the Office for the claims as currently pending. Additionally, in view of the arguments above, the claimed methods have utility. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

6.4 Interest of Equity

Applicants did not raise this issue with the response to the last Office Action dated 2/24/05, but will raise it now. An issue of equity and fairness is at hand with regard to this application in view of the public policy behind 35 U.S.C. § 154. Applicants have argued the combined rejection under 35 U.S.C. § 101 and 112, first paragraph (*i.e.*, the utility rejection) since the Office Action mailed April 23, 2003 (*i.e.*, now approaching the 3 year mark). Since then, Applicants have argued the utility rejection via replies to the Office Actions, have

interviewed the case with the Examiner and a Primary Examiner, have submitted an Appeal Brief, and have held discussions with the Examiner and Supervisory Examiner. Yet, by the Office's own admission it was not until the Office Action dated February 24, 2005, that the Office could precisely set forth the basis of its utility rejection ("In view of Applicants arguments, the Examiner has modified the rejections in order to more clearly set forth the Examiner's position. For instance, the instant rejections more clearly set forth the distinction between the rejection under 35 USC 101 and the rejection under 35 USC 112, first paragraph.") *See* Office Action dated February 24, 2005, page 18.

Applicants submit that taking nearly 2 years to crystallize the rejection over numerous papers is an undue burden on Applicants. This is exacerbated by the fact that the Office now does not even address how the rejections are maintained in view of the claim amendments and the new claims submitted in the response dated August 23, 2005. We are rapidly approaching the 3 year mark for the utility rejection.

Applicants respectfully request that the term of any patent that issues from this case be adjusted for some of the nearly 3 year period. Applicants do not request an extension based on the entire period, as Applicants note there were several extensions of time requested.[1] However, Applicants submit that should a patent issue from this application, the term of the patent should be adjusted under 35 U.S.C. § 154 in the interest of fairness and equity. Given the emphasis the Office is placing on review of applications and "a second pair of eyes" as repeatedly discussed by the Deputy Commissioners during their quarterly Customer Partnership Meetings, Applicants further submit that the chronology of events in this application is not in accordance with internal Patent Office policies of expediting and furthering prosecution of patent applications.

Applicants also note that although claims 1, 2, 6, 7, and 48-61 have been pending since their addition in February 3, 2003, the separate rejections under 35 U.S.C. § 112, first and second paragraph were never raised until *after* Applicants filed the Request for Continued Examination (RCE) at the behest and urging of the Patent Office. These new rejections raised the question in Applicants' minds whether this case should have withdrawn from Appeal and prosecution reopened by the Office, and not by Applicants.

Thus, for all the reasons stated above, Applicants put the Office on notice and formally request that a portion of the 2+ year period during which the application was

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[1] During the pendency of the 35 U.S.C. § 101 rejection, Applicants have requested a one-month extension of time with the Amendment and Reply dated August 25, 2003, a two month extension of time with the Notice of Appeal filed April 6, 2004, and a one-month extension of time with the Appeal Brief filed July 6, 2004.

prosecuted should be added to the term of the patent should a patent issue from the application.

7. **Rejection under 35 U.S.C. § 112, First Paragraph**

Claims 1, 2, 6, 7, and 48-67 also stand rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement for the reasons of record as set forth in the Office Action mailed February 24, 2005. *See* Office Action, pages 3-4.

Applicants traverse the rejection. Respectfully, it is unclear how the enablement requirement can be maintained ***for reasons of record***, when Applicants have amended the claims and introduced new claims without any explanation of *why* the arguments can remain the same. Additionally, Applicants note that the statement posited on page 9, of the "Response to Arguments" conflicts with the status of the rejection set forth on pages 3-4. There seems to be a change of rejection status indicated for the rejection on page 9 ("With respect to the rejection of claims under 35 USC 112, 1st paragraph (enablement) it is acknowledged that the claims have been amended such that relate to identifying an agent that inhibits the binding of ligand to HBM and/or Zmax1, thus rendering this aspect of the rejection moot."). Accordingly the rejection status of the claims under 35 U.S.C. § 112, first paragraph is unclear. As the alleged rejection is not clearly set forth, the finality of the action should be withdrawn. Also, Applicants maintain that a *prima facie* case of lack of enablement has not been adduced by the Office for the claims as currently pending. *See* M.P.E.P. § 707.07.

7.1 The methods are fully enabled for identifying reagents that modulate a lipid

On page 11 of the Office Action, the Office posits that the methods are not fully enabled for identifying reagents that modulate a lipid, because the art of record purportedly indicates that modulating a lipid is alleged as a complex process. S. Q. Ye et al., "Influence of genetic polymorphisms on responsiveness to dietary fat and cholesterol," 2000 *Am. J. Clin. Nutr.* 72: 1275S-1284S ("Ye") is cited by the Office for teaching that genes influence quantitative variations in plasma lipoprotein concentrations and cites to other polymorphisms in other genes which are also thought to be involved in modulating plasma lipid levels. Office Action, page 12. Apparently because of the complexity, the Office draws issues with the association of HBM to a particular lipid profile as not indicative that the claimed method is fully enabled for the full scope of identifying reagents that modulate lipids.

Applicants respectfully disagree with the Office's conclusion. As stated in the Appeal Brief filed July 2, 2004, on page 11:

> .... Ye *et al.* reviews a series of polymorphisms in various genes involved in lipid regulation. ....Ye *et al.* reports that studies of the effects of dietary cholesterol have not been consistent due to a series of confounding factors. This only means that it remains to be determined under what circumstances and for which polymorphisms dietary intervention is indicated.
>
> However, Ye *et al.* does not in any way cast doubt on whether those polymorphisms, or the HBM polymorphism, appear in genes related to lipid regulation. Ye *et al.* only shows that diet alone may not have a consistent effect. It certainly does not provide a reason to doubt the utility of the present invention. The question of whether a dietary change can affect lipid profiles simply has no bearing on the question of whether identifying a molecule that binds to a protein involved in lipid regulation (such as HBM or Zmax1) has credible utility as a method for identifying a molecule that is involved in lipid regulation.

Additionally, Applicants have amended the claims and introduced new claims. The claims are directed to a method of identifying or screening reagents to determine whether they bind to Zmax1 (or Zmax1 variant) and/or HBM, and whether they modulate a lipid in an animal or cell (*i.e.*, independent claims 1 and 6, respectively, and their respective dependent claims).

Enablement requires that the skilled artisan be able to make and use the invention based on the teachings of the specification and what was known in the art. As discussed *supra*, numerous drugs of different types exist that modulate lipid levels in humans. Therefore, reagents exist that modulate at least one lipid. Additionally, there are numerous animal models used for screening lipids, and which were known at the time. For example, dietary regimens in rabbits were known. Animal models exist for familial hypercholesterolemia. *See, e.g.,* T. Kita et al., 1987 "Probucol prevents the progression of atherosclerosis in Watanabe heritable hyperlipidemic rabbit, an animal model for familial hypercholesterolemia," *Proc. Nat'l Acad. Sci. USA* 84(16): 5928-5931. Alternatively, animal models can be transgenic models with specific genes knocked out like those of Magoori et al. (2003). Lipid analysis can be performed using various diets followed by blood testing of the subject, whether human or non-human. *See, e.g.*, the diet and tests used to analyze obtain angiographic measurements, histological measurements, cell culture studies and lipoprotein and plasma cholesterol levels using the New Zealand White rabbit model of atherosclerosis induced by femoral air desiccation with a high cholesterol diet. A. M. Lafont et al., "Effect of Alpha-tocopherol on restenosis after angioplasty in a model of experimental

atherosclerosis," 1995 *J. Clin. Invest.* 95: 1018-1025, at 1018-1020. Thus, the methods of screening for changes in lipid patterns were known at the time.

The complexity of lipid metabolism and the interaction of many genes, which is discussed by Ye, does not off set the tools that were available for screening changes in lipid pattern and the ability to detect these changes. The steps of the claimed method can be made and used given the disclosure of the specification and what was known in the art at the time. Accordingly, there is no *prima facie* case of lack of enablement as to the claims.

7.2 HBM and Zmax1 are involved in lipid modulation

On page 12, the Office asserts the following:

> Additionally, in order for the method to be able to identify molecules that modulate lipid regulation, it is imperative that HBM and Zmax1 are specifically lipid modulation. The specification discloses that HBM and Zmax1 are LDL-receptor family members, based on sequences similarity to known LDL-receptors as well as the association of the HBM polymorphism with a particular lipid profile. There is no disclosure in the specification which indicates either HBM or Zmax1 is a functional LDL receptor that is directly involved in lipid modulation. Therefore, additional experimentation is required.

Applicants' respectfully disagree with the Office's conclusion. As previously asserted: (1) Zmax1 binds to apoE; (2) Individuals expressing HBM have a different lipid profile than those expressing the wild type gene. This is disclosed in the specification on pages 83-85, 115, and 125-128. Applicants also state in the specification on pages 83-85 that Zmax1 and HBM are involved in lipid modulation. These facts and assertions coupled with *at least* the facts of Magoori et al. and Fujino et al., which show *inter alia* that LRP5 is involved directly in apoE regulation, all provide evidence that HBM and Zmax1 are involved in the modulation of a lipid.

7.3 Zmax1 Involvement in Multiple Pathways

On page 13, the Office asserts that "[t]he fact that HBM and Zmax1 may be involved in pathways unrelated to lipid modulation in combination with the fact that lipid regulation is a complex process involving many different factors indicates that HBM and Zmax1 may be functionally unrelated to lipid modulation, which is clearly indicative that additional experimentation would be required in order to fully enable the claimed invention."

Applicants again respectfully disagree with the conclusion asserted by the Office. The Fujino reference, which was reviewed by Nobel laureate recipients in the field of lipid

regulation, states that "LRP5 is a multifunctional receptor involved in multiple pathways, including bone development, cholesterol metabolism, and the modulation of glucose-induced insulin secretion." Fujino, at 229, right col. The multifunctional nature of the pathway is accepted by those artisans practicing in the field. It should likewise be accepted by the Office. The multifunctional nature of the pathway does not negate LRP5/Zmax1's or HBM's involvement in modulation of a lipid.

7.4 The Magoori and Fujino References

On page 10 of the Office Action, the Office Action states that the Applicants appear to concede that Magoori and Fujino do not disclose how LRP5 is involved in lipid regulation. Applicants do not concede that Magoori and Fujino do not disclose how LRP5 is involved in lipid regulation. Both references discuss LRP5 involvement in regulation of a lipid. For example, as discussed above, Fujino discusses that LRP5 directly and indirectly modulates apoE.

Therefore, for at least the above reasons, Applicants maintain that a *prima facie* case of lack of enablement has not been adduced as to the claims. Applicants respectfully request withdrawal of the rejection and allowance of the claims.

8. Response to Arguments

On pages 4 to 13 of the Office Action, the Office presented argumentation on both the combined 35 U.S.C. §§ 101 and 112, first paragraph rejections (*i.e.*, pages 4-9) and Applicants' prior responses thereto, as well as to the separate 35 U.S.C. § 112, first paragraph enablement rejection (pages 9-13). A response to the Office's argumentation is discussed in the appropriate sections above, as indicated.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

If any fees are required, or if a Notice of Appeal fee (and associated Notice of Appeal) is required to maintain pendency, the Office is asked to charge Deposit Account No. 50-0573. The Office can credit any overpayments to the Account.

Respectfully submitted,

DRINKER, BIDDLE & REATH LLP

Date: February 15, 2006

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